REMARKS

Reconsideration is requested.

The Examiner is requested to have the Patent Office enter the CORRESPONDENCE ADDRESS INDICATION FORM filed March 11, 2003 (copy attached) so that the undersigned may have access to the Patent Office electronic records relating to this application.

Claim 43 has been amended, and claim 58 canceled, without prejudice - obviating the claim objections noted on page 2 of the Office Action dated June 8, 2004.

The Section 112, first paragraph "written description", rejection of claims 43-62, is traversed. The pending claims are submitted to be supported by an adequate written description, for many of the reasons detailed in the Amendment of February 17, 2004, and repeated herein for completeness.

The indiscriminately reverse transcribing of the claims is supported by the specification, as will be appreciated by one of ordinary skill in the art. Contrary to the Examiner's assertions on the bottom of page 2 of Paper No. 25 (Office Action dated October 16, 2003), and page 3 of the Office Action dated June 8, 2004, the specification specifically describes at page 3, line 20, indiscriminate amplification of all types of fusion genes implicating the target gene. As noted in the previously submitted evidence, one of ordinary skill in the art well appreciated at the time of the present invention the method of anchored PCR for amplification of cDNA. Moreover, the specification describes, for example, at page 3, lines 19-20, the use of a single pair of primers for the anchored PCR to perform the indiscriminate reverse transcription of RNA.

The Examiner has commented on page 3 of the Office Action dated June 8, 2004 that "the specification does not support "indiscriminate" amplification, since the method requires a specific primer complementary to the target gene. That is, the specific primer would necessarily amplify a specific target gene, and therefore, this part of the amplification cannot be considered "indiscriminate"."

The Examiner has further asserted that the specification allegedly fails to describe the use of indiscriminate reverse transcribing because (1) "this citation is to a prior art reference from which Applicant distinguishes the instant invention", and (2) "this citation does not include the properties of the primers used for the indiscriminate amplification (e.g., using a primer comprising a "unique" 5' portion)." See, passage spanning pages 3-4 of the Office Action dated June 8, 2004.

The invention of claim 43, for example, recites at least five (5) steps. The first three recited steps of claim 43 refer to three primers which are inter-related in their action. The first three (3) steps of claim 43 describe a method of rapid amplification of cDNA ends, or RACE technique, with an "anchored primer", which was well recognized by one of ordinary skill in the art at the time of the present invention. See also, column 5, lines 23-32 of U.S. Patent No. 5,547,838, cited by the Examiner ("Thus, to both identify the breakpoint flanking sequences, and to define the orientation of transcription, Rapid Amplification of cDNA End **(RACE) technology** is preferably exploited to amplify sequences 3' or 5' to the AML1 gene (Frohman, M. A. et al., Proc. Natl. Acad, Sci. (U.S.A.) 85:8998-9002 (1988); Ohara, O. et al., Proc. Natl. Acad. Sci. (U.S.A.) 86.:5673-5677 (1989)). **These procedures are also known as "one-sided PCR" or "anchored-**

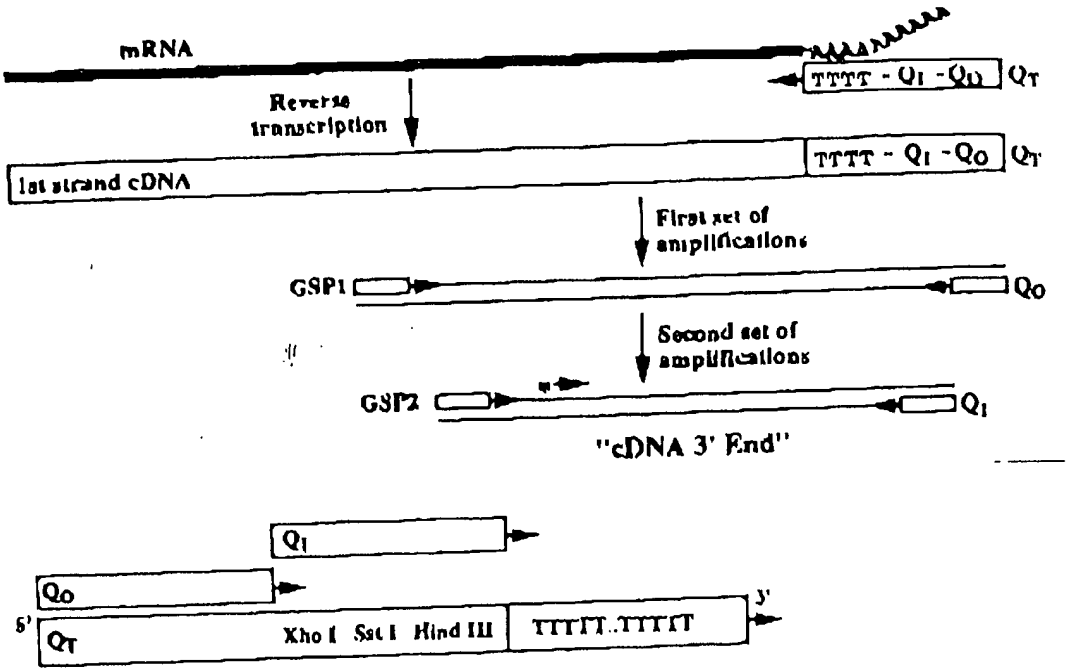
PCR," and facilitate the recovery of full-length cDNAs from rare transcripts." (emphasis added).

The first step of claim 43 requires " indiscriminately reverse transcribing RNA extracted from a patient sample with a first primer, said first primer being a random anchored primer, said reverse transcribing producing patient cDNA, said anchored primer comprising a unique 5' portion and a 3' random portion,". This step of indiscriminate reverse transcribing RNA with a random anchored primer was known in the art to be a useful means of producing patient cDNA. The RNA extracted from a patient in the first step of claim 43 is indiscriminately reverse transcribed with a first primer.

In a second step of claim 43, the patient cDNA produced in step (a) is amplified. The amplification of step (b) of claim 43 requires the use of a first pair of primers. The first pair of primers of the second step (b) of claim 43 comprise a second primer and a third primer. The first primer, second primer and third primer are distinct. The second step (b) of claim 43 states that the second primer is complementary to and bind specifically with cDNA of the target gene. The second step (b) of claim 43 states that the third primer is complementary to and binds specifically with a first part of the unique 5' portion of the anchored (i.e., first) primer.

The applicants have previously submitted a portion of a textbook titled "PCR PRIMER: A LABORATORY MANUAL" (Dieffenbach and Dveksler (Eds.) Cold Spring Harbor Laboratory Press, 1995) which was published prior to the applicants claimed priority date.

As has been previously explained by the applicants, the previously-filed "PCR PRIMER: A LABORATORY MANUAL", describes, in a section authored by Michael A. Froham (pp. 381-384, previously submitted), the following example of the RACE technique:



wherein 3' end partial cDNA clones are generated from mRNA which has been reverse transcribed using a "hybrid" primer (Q_T) that, in this example, consists of a 17 nucleotides of oligo (dT) followed by a "unique" 35-base oligonucleotide sequence (Q_1-Q_0) "which in many reports is denoted as an "anchor" primer." See, page 382 of Manual, line 30-31 after Figure 1.[1]

[1] The anchor poly-T tail in the schematic corresponds to a random sequence in the present invention

The "hydrid" primer of the above reproduction of the previously-submitted textbook reference is an exemplification of the first primer of step (a) of claim 43. This first primer of the claim, which is used to indiscriminately reverse transcribe RNA extracted from a patient sample to produce patient cDNA, does not include a specific primer or sequence complementary to the/a target gene, as suggested by the Examiner in the above-quoted passage of the Office Action dated June 8, 2004. Moreover, the "indiscriminate" aspect of claim 43 relates to reverse transcription of RNA, as opposed to the "amplification" of cDNA. The applicants do not disagree therefore with the Examiner's statement that "the specific primer would necessarily amplify a specific target gene, and therefore, this part of the amplification cannot be considered "indiscriminate"" however the Examiner is urged to appreciate that the claims do not require that the amplification of patient cDNA, according to step (b) of claim 43 is indiscriminate.

One of ordinary skill in the art will appreciate that claim 43, for example, requires in step (a) indiscriminately reverse transcribing which results in amplification of cDNA, and then amplification in a second step (b) with a pair of primers, wherein a second primer interacts specifically with a target gene and a third primer interacts with a portion (e.g., first part of the unique 5' portion) of the first primer. The third primer of the second step (b) of claim 43 therefore is schematically exemplified, for example, as

" [ ] Q_0" above.

A second pair of primers are used in the third step (c) of claim 43 in a nested amplification reaction. The second pair of primers includes a fourth primer and fifth

primer wherein the fourth primer is complementary to and binds specifically with the target gene at a position 3' to the second primer, and the fifth primer contains a sequence which binds to at least a portion of the first part of the unique 5' portion of the first primer.

Schematically, the fourth primer of step (c) of claim 43 and the fifth primer of step (c) of claim 43 may be represented, for example, by primers "GSP2 [ ] " and " [ ]Q_1" , respectively, in the above reproduction of the textbook reference.

The applicants submit that, in view of the above, the description of "anchored PCR" being part of the method of the present invention at page 3, lines 19-20, to "indiscriminately amplify all types of fusion genes implicating the target gene" in the following passage of the specification, taken with the specification as a whole (such as the teaching of page 4, lines 3-11) and the advanced level of skill in the art at the time the application was filed, one of ordinary skill in the art would appreciate that the applicants were in possession of the presently claimed invention at the time the application was filed. One of ordinary skill in the art would believe the specification adequately describes the presently claimed invention.

For completeness, the applicants do not agree that the description at page 3, lines 19-20 of the specification is "to a prior art reference from which Applicant distinguishes the instant invention" as asserted by the Examiner at page 3 of the Office Action dated June 8, 2004. Rather, the applicants describe that "The solution contributed by the [i.e., the present] invention is based on the production of an anchored PCR, ..., to indiscriminately amplify ...". The prior paragraph spanning lines 11-17 of page 3 of the specification describe "A multiplex PCR technique [which] was recently

proposed ... But this is still a sophisticated technique, becoming increasingly difficult ..., and in addition, it requires a very expensive equipment ..." The "solution" to these problems of the prior methods therefore provided by the presently described method involves the use of anchored PCR to indiscriminately amplify.

As noted above and previously, and as is made clear in the previously-submitted textbook reference, anchored PCR, as described in the present specification, is well known in the art as the "Classic RACE" technique. The classic RACE technique is generally described in steps (a)-(c) for example of claim 43.

The above, and comments of record, are believed to also be responsive to the Examiner's comments on pages 4-6 of the Office Action of June 8, 2004. The applicants note that the present claim language was added in response to the Examiner's previous rejection of the applicants generally recited use of anchored PCR. The applicants have demonstrated, by reference to the above-noted textbook, that PCR using an "anchored" primer was known at the time of the present invention by those of ordinary skill in the art as "Classic RACE".

It is well established that:

"It is not necessary that the claimed subject matter be described in *ipsis verbis* to satisfy the written description requirement of 35 USC 112." Nelson v. Bowler et al. (BdPatApp&Int) 1 USPQ2d 2076, 2078 (6/19/1986).

In Nelson v. Bowler, the Board held that Nelson's specification provided a sufficient written description of a species of the Count even though the specification only provided a subgenus of compounds within the Count. The Board noted that "The issue

is whether the Nelson specifications convey clearly to those skilled in the art that Nelson invented the compounds at issue." Id.

Moreover, the Court in In re Filstrup, Jr. (CCPA 1958 251 F2d 850, stated the following with regard to an applicants inherent support for a claim recitation:

> "It is true that the mere fact that one following the disclosure of an application might produce a structure satisfying a claim is not, in itself, a sufficient basis for permitting an applicant to make that claim (Brand v. Thomas, 25 C.C.P.A. (Patents) 1053, 96 F.2d 301, 37 USPQ 505) but, as was pointed out in Binstead et al. v. Littmann et al., 44 C.C.P.A. (Patents) 839, 242 F.2d 766, 113 USPQ 279 , a sufficient basis is provided if "the specification is so worded that the necessary and only reasonable construction to be given the disclosure by one skilled in the art" is one which will lend clear support to the claim. In our opinion the latter condition exists in the instant case."

Finally, the Court stated as follows in In re Herschler, 200 USPQ 711, 717 (CCPA 1979):

> "The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him; how the specification accomplishes this is not material. In re Smith, 481 F.2d 910, 178 USPQ 620 (CCPA 1973). The claimed subject matter need not be described in haec verba to satisfy the description requirement. In re Smith, 59 CCPA 1025, 458 F.2d 1389, 173 USPQ 679 (1972). It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations. In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973)."

The applicants submit that one of ordinary skill in the art would recognize from the disclosure that the applicants invented the claimed invention.

Reconsideration and withdrawal of the Section 112, first paragraph "written description", rejection of claims 43-62 is requested.

To the extent not obviated by the above amendments, the Section 112, second paragraph, rejection of claims 43-62 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and previously submitted evidence.

Claim 52 has been amended above to obviate the basis of rejecting claim 52 under Section 112, second paragraph stated in ¶(E) on page 8 of the Office Action dated June 8, 2004. The applicants acknowledge, with appreciation, the Examiner's careful review of the claims. Entry of the amendments will at least reduce this issue for appeal. Entry of the amendments is requested.

The Examiner's comments in ¶¶ (A)-(D) on pages 7-8 of the Office Action dated June 8, 2004 are addressed in the above and previously submitted evidence which demonstrates that one of ordinary skill in the art is able to understand and practice the recited method steps. The Examiner is further requested to review U.S. Patent No. 5,547,838, cited by the Examiner, and the Examiner's interpretation of the same on, for example, pages 12-13 of the Office Action dated June 8, 2004. The Examiner's obviousness rejections based on the cited patent appear to be contrary to at least the Examiner's Section 112, second paragraph, rejection.

With regard to the Examiner's comment in ¶(E) on page 8 o the Office Action dated June 8, 2004, the applicants note that step (c) of claim 43, for example, requires that the second collection of amplified products contain detectably labeled nucleotides incorporated in to the products during amplification. One of ordinary skill in the art will appreciate that this second collection of amplified cDNA contains detectably labeled

cDNA. The metes and bounds of the claimed invention will be clear to one of ordinary skill in the art.

The applicants respectfully disagree with the Examiner's comment in ¶(F) on page 8 of the Office Action dated June 8, 2004 as ¶(c) of claim 43 states " said second collection of amplified products further comprising detectably labeled nucleotides incorporated in to said products during amplification". Claim 45, which depends from claim 43 refers back specifically to "said detectably labeled nucleotides". Similarly, claim 51, which depends from claim 49, which depends from claim 43, refers back specifically to "said detectably labeled nucleotides". Antecedent support for the recitations of claims 45 and 51 are provided in claim 43, from which each claim directly or indirectly depends.

Withdrawal of the Section 112, second paragraph, rejection of claims 43-62 is requested.

Entry of the above amendments, which cancels claims 58 and 60, will make moot the Section 102 rejection of claims 58 and 60 over Morris (U.S. Patent No. 5,770,421). Claim 61, which was dependent from claim 58 and indicated as allowable over Morris, has also been rewritten above as an independent claim to include the details of now canceled claim 58. The dependencies of claims 59 and 62 have been amended accordingly above. Entry of the above amendments will there fore reduce the issues for appeal by making moot the Section 102 rejection of claims 58 and 60 over Morris. The amendments have been made to reduce the issues for appeal and without prejudice. A Notice of Appeal was filed October 8, 2004. Entry of the above amendments is requested.

The following Section 103 rejections are traversed:

(A) the Section 103 rejection of Claims 43-48 and 57 over Nisson (U.S. Patent No. 5,547,838) in view of Holtke (Cellular and Molecular Biology, 1995, 41(7), 883-905);

(B) the Section 103 rejection of claims 49-54 over Nisson in view Holtke and Felix (U.S. Patent No. 6, 368,791);

(C) the Section 103 rejection of claim 55-56 over Nisson in view of Holtke, Felix and Kaneko (Genes, Chromosome and Cancer (March 1997) 18:228-231); and

(D) the Section 103 rejection of 62 over Nisson in view of Holtke, Felix and Stratagene Catalog (1988).

Reconsideration and withdrawal of the Section 103 rejections of the various claims are requested as, by the Examiner's admission, the primary reference of rejections (A) through (D) above, e.g., Nisson, fails to teach detecting any detectably labeled cDNA from a second collection of amplified products, as required by the presently claimed invention. See, pages 13 to 14 of the Office Action dated June 8, 2004. The applicants believe the primary patent fails to fairly suggest such a detection or incorporating a detectable label. Moreover, the secondary references, individually or in combination, are not believed to cure this deficiency. Withdrawal of the above-noted Section 103 rejections is requested.

The Section 103 rejection of claim 59 and 61 over Morris, Holtke and Stratagene Catalog, is traversed.

The Examiner's reliance on seemingly general primers as providing the primers of the claimed kits is, with due respect, submitted to be inappropriate. The Examiner

will appreciate that Morris teaches, at best, two specific primers, one for NPM and the other for ALK, neither of which are an anchored primer according to the presently claimed invention. Moreover, the probes identified by the Examiner in column 20, lines 42-49 of Morris are themselves labeled whereas in the presently claimed invention the probes are not required to be labeled. There is no motivation in the art to alter the teaching of Morris to make the presently claimed invention.

Withdrawal of the Section 103 rejections of the noted claims is requested.

Entry of the above amendments, at least to reduce the issues for appeal, is requested. Entry of the above amendments and allowance are requested. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Respectfully submitted,

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